Remarks

Status of the Claims and Support for the Amendments to the Claims

By the foregoing amendments, claim 74 has been canceled without prejudice or disclaimer. Claims 1 and 73 are sought to be amended. Support for the amendments to claims 1 and 73 can be found throughout the specification, particularly at page 5, line 29 through page 6, line 12; and throughout Examples 8 and 9. Therefore, these amendments introduce no new matter. Upon entry of the foregoing amendments, claims 1-4, 7, 8, 12, 69, 73 and 75-76 are pending in the application, with claims 1 and 73 being the independent claims.

Summary of the Office Action

In the Office Action dated June 9, 2006, the Examiner has made one rejection of the claims. Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

The Rejection Under 35 U.S.C. § 103(a) Over Papahadjopoulos, In View of Spragg, Martin, Ladner, Wang, Xu and Scherman

In the Office Action at pages 3-6, section 5, the Examiner has rejected claims 1-4, 7, 8, 12, 69, and 73-76 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Papahadjopoulos *et al.*, U.S. Patent Application No. 2004/0209366 (hereinafter "Papahadjopoulos"), in view of Spragg *et al.*, *Proc. Natl. Acad. Sci. 94*:8795-8800 (1997) (hereinafter "Spragg"), Martin *et al.*, *J. Biol. Chem. 257*:286-288 (1982) (hereinafter "Martin"), Ladner *et al.*, U.S. Patent No. 4,946,778 (hereinafter "Ladner"), Wang *et al.*,

Bioconjugate Chemistry 8:878-884 (1997) (hereinafter "Wang"), Xu *et al.*, *Human Gene Therapy 10*:2941-2952 (1999) (hereinafter "Xu") and Scherman *et al.*, U.S. Patent No. 6,200,956 (hereinafter "Scherman"). By the foregoing amendments, claim 74 has been canceled. Hence, this rejection has been rendered moot as it may have applied to this claim. Applicants respectfully traverse this rejection as it may apply to the remaining claims.

The Examiner contends that Papahadjopoulos discloses the use of a targeting moiety such as antibody fragments, including scFvs, linked to cationic liposomes. The Examiner further contends that Papahadjopoulos discloses that the liposomes can be used to deliver tumor suppressor genes, and that the liposomes may comprise helper lipids DOPE and cholesterol. The Examiner also states the Papahadjopoulos discloses the use of a ratio of antibody:lipid to be 15.6 μg of scFv to 1 μmol lipid, which falls within the w:w range recited in present claim 1. Applicants respectfully disagree with these contentions.

The Examiner states that Papahadjopoulos does not disclose that the scFvs are directly conjugated to the cationic immunoliposome via a sulfur atom that was part of a SH group at the carboxy terminus of the scFV, including wherein the scFv is covalently bound to DOPE linked to MPB, nor wherein the scFV is capable of binding to a transferrin receptor. The Examiner relies on the disclosures of Spragg, Martin, Ladner, Wang, Xu and Scherman to cure these deficiencies.

The Examiner states that Spragg discloses the preparation of targeted, cationic immunoliposomes by modifying an antibody against a target with a succinimidyl-S-acetulthioacetate. The Examiner contends that Martin discloses coupling of Fab' fragments to liposomes via a sulfur atom on the Fab' using MPB. The Examiner states that Martin discloses that it is possible to link any thiol-containing protein ligand to MPB-PE containing

liposomes. The Examiner also contends that Martin discloses that the absence of the Fc region of the antibody is desirable to eliminate the possibility of Fc-mediated binding and complement activation.

Next, the Examiner states that Ladner discloses that the use of single chain antibodies such as scFV has advantages over the use of conventional antibodies or Fab fragments, such as smaller size, greater stability, etc. The Examiner further states that Ladner discloses that all of the uses that the prior art has envisioned for monoclonal or polyclonal antibodies can be considered for single chain Fv fragments.

The Examiner contends that Wang discloses generation of an scFv with a carboxy terminal cysteine for the purpose of covalently linking the scFv-cys to a toxin through a disulfide bond. The Examiner further states that Wang discloses the advantages of using scFvs rather than intact antibodies.

With regard to Xu, the Examiner states that this reference discloses the use of transferrin-cationic liposomes for delivery of wild type p53 to various tumors. Finally, the Examiner contends that Scherman discloses immunoliposomes comprising transferrin and transferrin antibodies/fragments as targeting molecules for cells such as tumor cells.

The Examiner concludes that it would have been obvious for one of ordinary skill in the art to combine these seven disclosures to have made the immunoliposomes disclosed in Papahadjopoulos, for delivery of a p53 gene, using a scFv antibody fragment with a specificity for transferrin directly conjugated to the liposome by coupling the scFv to Cys and mixing the scFv at the ratios disclosed in Papahadjopoulos, but using the direct conjugation methods disclosed in Spragg and Martin rather than the linker system disclosed in Papahodjopoulos. The Examiner contends that it would have been obvious to combine

the disclosures of the cited references based one a complex series of assumptions and connections, and centered around the contentions that Wang discloses that it is advantageous to use scFvs rather than intact antibodies and that Ladner discloses the advantages of using scFvs and that "they may be used for any application that antibodies or other variable region antibody fragments are used for." Office Action at page 6, lines 17-18. Applicants respectfully disagree with the Examiner's conclusion and the contentions on which they are based.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). The Examiner has not met this burden.

As stated in Applicants' Reply to Office Action filed on March 30, 2006, the disclosure of which is incorporated herein by reference in its entirety, Applicants respectfully submit that Papahadjopoulos does not disclose a nucleic acid-cationic immunoliposome complex in which an scFv antibody fragment is directly conjugated to the liposome via a sulfur atom which was part of a sulfhydryl group at a carboxy terminus on the antibody fragment as recited in present independent claims 1 and 73. All of the Examples in Papahadjopoulos disclose the use of a polymer (PEG) linker (Maleimido-propionylantido-PEG-diastearoylphosphatidylethanolamine (Mal-PEG-DSPE)) to link the antibody fragment

to the liposome vi a hydrophobic interaction. Papahadjopoulos thus does *not* disclose direct conjugation of the antibody to the liposome, as required in the presently claimed invention.

In addition, Applicants respectfully submit that Papahadjopoulos does not disclose the 1:5 to 1:40 w/w ratio of protein:lipid recited in present claim 1. The Examiner refers to Example 7 of Papahadjopoulos, stating that the liposome utilized in this Example is made of the same constituents as the liposome in Example 6, and contends that 1 μmol of lipid is equal to 0.21 mg of lipid, and therefore the ratio the ratio of antibody fragment to lipid of 15.6 μg:1 μmol (or 1 μg:64 nmol), falls within the scope of claim 1. Applicants respectfully disagree with the Examiner's contentions.

As set forth in Applicants' previously filed reply:

> The wt:wt (e.g, μg) ratios of scFv:liposome in present claim 1 of
> 1 μg:5μg to 1 μg:40 μg, correspond to molar ratios of
> 0.036 nmol protein:7 nmol lipid to 0.036 nmol protein:56 nmol lipid.
> Or, utilizing wt:mol values, the ratios of present claim 1 correspond to
> 1 μg protein:7 nmol lipid to 1 μg protein:56 nmol lipid.

This conversion clearly demonstrates that the ratio of 1 μg of protein:64 nmol lipid recited in Example 7 of Papahadjopoulos falls outside the scope of present claim 1.

To further confirm that the ratios disclosed in Papahadjopoulos do not fall within the scope of present claim 1, the ratio of 15.6 mg protein:1 μmol lipid can be converted to a wt:wt ratio as follows.

Assuming that the lipid composition utilized in Example 7 of Papahadjopoulos is the same composition set forth in Example 6, this composition comprises:

1-palmitoyl-2-oleoyl phosphatidylcholine (POPC) (MW:760.09g/mol);

Cholesterol (MW:386.66 g/mol); and

Methoxypolyoxyethyleneglycol-derivatized disearoyl phosphatidylethanolamine (DSPE-PEG) (MW:1900 g/mol (PEG) + 748.08 g/mol (DSPE) ≅ 2648.08 g/mol).

The lipids are mixed at a molar ratio of 30:20:3 (POPC:Cholesterol:DSPE-PEG).

Utilizing the 1 μmol of lipid from Example 7, the molar amounts of each component would therefore be:

> 0.569 μmol POPC:0.379 μmol cholesterol:0.0569 μmol DSPE-PEG).
> Converting these molar values to weights (based upon the molecular weights above) 0.433 mg POPC:0.147 mg cholesterol:0.151 mg DSPE-PEG
> The total weight of 1 μmol of liposome is therefore 731 μg of lipid.
> The ratio of 15.6 μg of protein: 1 μmol lipid utilized in Example 7 is then 15.6 μg protein:731 μg of lipid, which reduces to 1 μg protein: 48.7 μg lipid.

This wt:wt ratio of 1:48.7 is clearly outside of the range disclosed in present claim 1 of 1:5 to 1:40.

Hence, Papahadjopoulos does not disclose the protein:lipid ratios recited in present claim 1, and hence, is clearly deficient as a primary reference on which to base a *prima facie* case of obviousness with regard to present claim 1. Applicants submit that the disclosures of Spragg, Martin, Ladner, Wang, Xu and Scherman also do not disclose such ratios, and hence, to not cure these deficiencies noted in Papahadjopoulos.

Furthermore, Applicants respectfully submit that, as the Examiner has stated (see Office Action at page 3, third paragraph), Papahadjopoulos does not disclose the complex of present claim 73, in which the scFv antibody fragment is directly conjugated to the liposome via a sulfur atom which was part of a sulfhydryl group at a carboxy terminus on the antibody fragment. Hence, Papadopoulos is clearly deficient as a primary reference on which to base a *prima facie* case of obviousness with regard to present claim 73. Applicants respectfully

submit that these deficiencies are not cured by the disclosures of Spragg, Martin, Ladner, Wang, Xu and Scherman, alone or in combination.

Spragg only discloses the use of full length antibodies ("Murine mAb H18/7, an IgG 2α antibody," page 8796, second column, lines 5-6), not scFv antibody fragments. There is no indication in Spragg that scFvs could or should be linked to cationic liposomes using any method. Applicants respectfully submit that the ordinarily skilled artisan would not be motivated to utilize scFvs in place of full length antibodies due to their differences in size, structure and properties. In addition, Applicants submit that the ordinarily skilled artisan would clearly not have a reasonable expectation of success to make such a substitution absent clear and explicit disclosure of how to make such a modification.

Martin discloses only complexes with Fab' fragments, not scFvs, and provides no disclosure that scFv fragments could be linked to liposomes, much less what ratios of such a fragments to liposome would be useful. As stated in Applicants' previously filed reply, an Fab' is quite different from an scFv. The two fragments have different structures and sizes and different behaviors and uses. Furthermore, Martin does not give any guidance as to what ratio one would use with an scFv rather than an Fab'. This lack of guidance is significant, especially because of the difference in size of the two types of fragments (Fab' are about 55-60 kDa; scFv are approximately 24-28 kDa). The ordinarily skilled artisan, guided only by the disclosure of Martin, could not expected to be able to simply replace one type of antibody fragment with the other. Hence, the Examiner has not provided sufficient motivation, or a reasonable expectation of success, to utilize scFvs in the methods disclosed in Martin which are directed to coupling of Fab' fragments. In addition, as noted in Applicants' previous reply, the ratio of Fab':lipid disclosed Martin is very different from the

ratio required in present claim 1, and Martin provides no motivation, much less a reasonable expectation of success, to modify that ratio such that it would fall within the scope of claim 1.

The Examiner contends that Ladner discloses that all of the uses that the prior art has envisioned for monoclonal or polyclonal antibodies, or for variable region fragments thereof, can be considered for the scFvs disclosed therein. While Ladner make such a statement, Ladner is limited to computer-based systems for developing antibody fragments. Simply disclosing methods for preparing antibody fragments does not provide the support required to establish a *prima facie* case of obviousness. A statement that scFvs could be used in applications where mono- or polyclonal antibodies have been used in the past does not, absent more, provide a motivation or even a suggestion to utilize such molecules in the preparation of immunoliposome complexes. Ladner does not disclose, let alone enable, the preparation of immunoliposome complexes comprising scFvs, and hence, does not render obvious the presently claimed invention.

The disclosure of Wang is limited to conjugation of an scFv to a toxin, not a lipid, and at a ratio well outside the protein to lipid ratio set forth in claim 1, as discussed in Applicants' previous reply. With regard to Xu, Applicants note that the reference does not disclose the use of scFv fragments, disclosing instead complexes in which liposomes are complexed with transferrin, as a targeting ligand. Transferrin and an scFv, such as the transferrin receptor scFv used in examples of the present application, are very different molecules, with different sizes and very different functions. One of ordinary skill in the art would not expect that one could be substituted for the other, and the Examiner has provided no evidence of any motivation or suggestion of such a substitution.

Finally, Scherman does not disclose conjugation of scFv fragments to liposomes. The reference does not disclose direct conjugation, including conjugation via a sulfhydryl group, nor what ratios of protein and lipid would be required to prepare the cationic immunoliposomes of the present invention.

Applicants respectfully submit that the ordinarily skilled artisan would not have been motivated to combine the disclosures of these references as required by the Examiner. In order to attempt to show the requisite motivation, the Examiner has set forth a series of *ten* steps (increased from the eight steps set forth in the previous Office Action) required to precisely combine selected portions of the *seven* cited references to produce the presently claimed invention. Applicants respectfully submit that the ordinarily skilled artisan would have found no motivation to combine the portions of the cited references, selectively excerpted by the Examiner, using this complex path required by the Examiner. Indeed, this highly selective approach used by the Examiner, in which portions of the cited references are chosen piecemeal and combined with each other while excluding the remainder of each reference, is the very *epitome* of hindsight reconstruction.

Applicants respectfully submit, as set forth in their previous reply, it is only with the value of hindsight gleaned from the present application that one could find that the cited references suggest immunoliposomes comprising scFv antibody fragments. As the Federal Circuit has held numerous times, a hindsight analysis such as that employed by the Examiner in the present case is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require

selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *In re Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure."). *See also*, *Ex parte Haymond*, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996) ("[The Examiner] may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis"). Thus, the Examiner's hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness.

Furthermore, even assuming *arguendo*, that the references do provide the requisite suggestion or motivation, the references provide no practical guidance as they do not suggest what ratios could be, or should be, used to form a stable, scFv-liposome complexes with biological activity. As set forth above and in Applicants' previous reply, the ratios set forth in the references (including Papahadjopoulos) are significantly different from the ratios found to be useful by the present inventors and that are set forth in present claim 1. Applicants respectfully submit that the Examiner has pointed to nothing that would have motivated the ordinarily skilled artisan to make the claimed combination. Moreover, it would require an undue amount of experimentation to arrive at the complex and ratios set

forth in claim 1 of the present application. Thus, there cannot be a reasonable expectation of success to make such a combination based on the cited references.

Applicants respectfully submit that disclosure of coupling full length antibodies or Fab' fragments to liposomes does not lead one of skill in the art to the conclusion that scFvs could also be coupled to liposomes in a similar manner. Therefore, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully submit that claims 1-4, 7, 8, 12, 69 and 73-76 are not rendered obvious by the disclosures of Papahadjopoulos, In View of Spragg, Martin, Ladner, Wang, Xu and Scherman, alone, or in combination. Hence, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, rendered moot or otherwise overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and objections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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